ORIGINAL ARTICLE

The Hormonal Levels of Estrogen in Second and Third Trimesters of Gestational Diabetes Mellitus Patients with or without Family History

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ABSTRACT

Gestational diabetes mellitus (GDM) is a severity of varying degrees of glucose intolerance which is first recognized during pregnancy. Generally it has few symptoms and it is most commonly diagnosed in pregnancy by screening. In pregnancy due to Insulin resistance both fetal and maternal complications occurs . In physiological adaptations of pregnancy the level of numerous hormones generally are increased. In the present study the responses of the pertinent hormone of the pregnancy, estrogen have been investigated in gestational diabetes and non-GDM subjects specially in context of positive and negative family history in second and third trimester. The present cross sectional 2 stage study with non-probability convenient sampling was done in Arif Memorial Teaching Hospital, Lahore and Hameed Latif Hospital, Lahore. One hundred and ten females from rural and urban areas of Lahore were the study population, out of which 55 had GDM and 55 were controls/non-GDM. After taking their consent, general data of the pregnancy and blood samples were taken. The hormones were estimated by ELISA with specific monoclonal antibodies. The results were analyzed in relation to GDM, non-GDM, positive family history in second and third trimester. In second trimester estrogen were found increased several times in GDM than non GDM subjects. These increases were varied to 8 times and 11 times in positive and negative family history subjects respectively and compared to non GDM respective control subjects. In third trimester also the response of estrogen was numerous times increases in GDM than non-GDM. The pattern of this increase was varied in positive and negative family history subjects. The analysis of results of the estrogen within GDM and non-GDM category and between the semesters has shown some noticeable and statistically noticeable results. The significantly varied responses of estrogen in different family history of the subjects and in different trimester clearly demonstrate that it is one of the cause of induction of insulin resistance in GDM.

Keywords: Estrogen, Gestational Diabetes Mellitus, Family History

INTRODUCTION

Pregnancy begins from the 1st day of the woman's last menstrual cycle and is divided into three trimesters, each lasting three months[1]. Pregnancy starts from conception and ends with birth of fetus.

The metabolic abnormalities which results in diabetes mellitus, as a result of which concentration of glucose increases in blood which is termed as hyperglycemiaisdue to defective secretion of insulin [2].

Gestational diabetes mellitus is the level of glucose metabolism abnormality which is usuallyrecognized in the phase of gestation and it is recognized when the beta cells of pancreas not secreting enough insulin to overcome the insulin resistance and this phenomenon occur in 7-8% of all women bearing child[1]. Defective function of beta cell and resistance of insulin play role in GDM. Gestational diabetes is reported in second and third trimester and disappears after the delivery of fetus[3]. It refers to the appearance of increased blood sugar levels in a pregnant lady previously not suffering from diabetes mellitus. The majority of such females progress to overt non insulin dependent diabetes mellitus with time. 30000 to 90000 individuals suffering from gestationaldiabetes per year reported in US[4]. The stress of pregnancy is the important factor to develop gestational diabetes mellitus as it uncovers the susceptibility of genes to develop non insulin dependent diabetes mellitus**.** Chances of development of non insulin dependent diabetes in females with gestational diabetes occur in later life[5]. Glucose tolerance deteriorates in human pregnancy. Glucose intolerance screening is usually donearound 24–28 weeks of gestation. Basal glucose concentrations decrease with advancing trimesters in females developing GDM. In 2nd and 3rd trimesters, hepatic glucose production was reported to be increased in females with gestational diabetes[6]in comparison with a control group whereas no difference was noted in either fasting or random (hepatic) glucose concentration in a study reported byCatalano[7]. Gestational diabetes is mostly diagnosed by screening during second and third trimesters of pregnancy as it has generally few symptoms. Depending on the population studiedgestational diabetes affects 3-10% of pregnancies[8].

It is often reported that females with positive family history of diabetes mellitus have more chance to develop metabolic disorder. So, family history of diabetes has certain risk factors like fat deposition[9] in abdomen, increase body weight and age. Family History mainly influences the incidence of gestational diabetes mellitus along with trimesters of pregnancy. Women with positive family history having gestational diabetes have more chance to develop type 2 diabetes.O'Sullivan[10] reported in a study that in pregnancy obese females have more chance to develop GDM then lean females. Long termhyperglycemia in pregnancy leads to both maternal and fetal complications.

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Long-term consequences of hyperglysemia include increased risk of glucose intolerance, diabetes and obesity[11]. Thus it is analyzed that trimesters along with positive family history in pregnancy influences the gestational diabetes mellitus.

In females estrone (E1), estradiol (E2) and estriol (E3) are three main naturally occurring estrogens and acts as a growth hormone for reproductive organs. Estradiol, in conjunction with progesterone, prepares the endometrium for implantation and are needed before the progesterone exposure in the luteal phase [12].

As pregnancy advancesinsulin resistance occurs in peripheral tissues due to raised levels of estrogen, Human chorionic sommatomammotropin (hCS), prolactin, cortisol and progesterone .During the middle phase of the gestation the hormonal changes and changes in metabolism during pregnancy result in glucose intolerance[13]. In the early phase of a non-diabetic pregnancy, insulin action is enhanced by estrogens and progesterone and glucose concentration tend to decline[14]. Later with increasing weeks of gestation insulin action resists and leads to increased levels of blood sugar levels.

Estradiol is recognized as the dominant estrogen and is present at high levels during pregnancy[15]. The marked rise in estrogens during pregnancy is of interest, as it occurs as collaboration between the maternal and fetal metabolism[16]. The various metabolites in this process are subsequently converted into estrone and estradiol and secreted back into the maternal circulation[15]. This gives rise to the concept of the fetoplacental unit as a site of hormone production during pregnancy.

Fetal growth regulation, parturition onset, placental formation of steroid, synthesis of glycoprotein, neuropeptide production and the intonation of lipid metabolism of mother, all the above mentioned are influenced by estrogen[17]; increase concentration of plasma lipid is the metabolic change which occur during second and third trimester of gestation is also due to estrogen[18].The estrogen production and its concentration in circulation varied in different phases of pregnancy. Estrogen production begins to increase rapidly once the placenta is large enough to take over the function of the corpus luteum that is in second trimester of pregnancy[19]. From this point onward, concentrations continuously rise until 39th to 40th week of pregnancy, reaching levels 3 to 8 times higher than in the non-pregnant state. It was found in a study that estradiol levels were 16 times higher at term than first trimester of pregnancy [20]. The enormous increase in the hormones the adaptability based on many complex interactions. There is likely that this adaptability in GDM compare to the normal pregnancy.

The present study has been carried out with the objectives of determining the circulatory levels of estrogen in GDM and non-GDM subjects with specific reference to the family history of diabetes in relation to second and third semester.

MATERIALS AND METHODS

It was cross-sectional 2 stage study. Total 110 subjects for sampling. From September, 2013 to February, 2014 were collected from Arif Memorial Teaching Hospital, Lahore and Hameed Latif Hospital, Lahore. Among 110 samples 55 samples were pregnant with gestation diabetes mellitus and other 55 samples belong to normal pregnant females. 55pregnant females without GDM and labeled as (Control). Remaining 55 were pregnant with GDM and labeled as (GDM). Selections of samples were made on inclusive and exclusive criteria. Inclusive criteria includes; Gestation week more than 12 weeks (2nd and 3rd trimesters only). On the other hand patients were excluded on the following criteria; Cushing syndrome, Cushing disease, pre-eclampia, liver disease, renal disease, cardiac disease, sepsis, recent surgery or history of trauma, on exogenous corticosteroid therapy, endocrine disorders. Pregnant females of 2nd and 3rd trimester were selected and classified as pregnant females with GDM and pregnant females without GDM, Personal, obstetric history, family history for diabetes mellitus, last menstrual period (LMP),gestational diabetes time period, predisposing factors with previous pregnancies, in case of multigravida, life style, educational status and general physical examination were recorded on questionnaire.

Methods& Biochemical Analysis: Five milliliter (ml) of blood sample was collected in disposable syringes from the pregnant females by venipuncture with aseptic measures. The blood was allowed to clot and then centrifuged, serum was separated and stored in serum cups at a temperature of -20 ^{0}C for assessment of Serum Estradiol level. All the tests were done in duplicate by ELISA technique using Access Bechman Coulter (USA).

Statistical Analysis: In the comparisons of various groups mean, standard deviation and standard error were calculated and the significance of the difference between the groups was determined with 2 sample t- test. The significance of the difference was taken atp ≤ 0.05.

The correlation between the different parameters was analyzed by SPSS for further elucidation of the results. The significance of correlation was taken atp ≤ 0.05

RESULTS

The hormones levels of estradiol were assayed in gestational diabetic (GDM) subjects in relation to the trimester and family history. The observations were made in second and third trimester of gestation in GDM andin normal or non-diabetic women (taken as control group). The categories of family history were distinguished as positive family history and negative family history.

SECOND TRIMESTER

GDM with positive family history: The mean circulatory level of estradiol was 20078.66±767.47pg/ml in the gestational diabetics with positive family history. The hormone concentration was 2619.654±949.66 pg/ml in normal pregnant subjects however with positive family history. A marked increase in the estradiol levels had been observed in GDM that was almost 08 times greater than the control subjects. It was highly significant statistically ($p<0.001$).(Table 1).

GDM with Negative family history: The circulatory value of estradiol level was 15525±1874.36 pg/ml in the gestational diabetics with negative family history. The hormone concentration was 1465.35±704.66 pg/ml in the non-diabetics normal pregnant subjects with negative

family history. A marked increase in the estradiol levels had been observed in GDM that was almost 11 times greater than control subjects. It was significant statistically (p<0.001)(Table 1).

GDM with different family history: The estradiol mean value was 20078.66 ± 767.47 pg/ml in the second trimester gestational diabetics with positive family history. The hormone concentration was 15525 ± 1874.36 pg/ml in the second trimester gestational diabetic subjects with family history negative. An increase in the estradiol levels had been observed in second trimester gestational diabetics with positive family history that is almost 29 % greater than with negative family history. It is highly significant statistically (p<0.018).(Table 1).

Non-GDM with different family history: The estradiol mean value was 2619.65± 949.67 pg/ml in the second trimester non- diabetics with positive family history. The hormone concentration was 1465.36±704.66pg/ml in the non-diabetic subjects with family history negative. An increase in the estradiol levels had been observed in second trimester non-diabetics with positive family history that was almost 78 % greater than with the family history negative. It was not significant statistically (p value 0.371) (Table 1).

Table 1: Comparison of estradiol according to 2nd trimestergestational diabetics and family history

2nd trimester Group	N	Mean	SEM	t-test	p-value
Diabetic family history positive.	15	20078.6	767.4	13.91	<0.001*
Non -diabetic family history positive	18	2619.65	949.6		
Diabetic family history negative	10	15525	1874.36	7.72	<0.001*
Non-diabetic family history negative	13	1465.35	704.66		
Diabetics family history positive	15	20078.7	767.47	2.55	0.018*
Diabetics family history negative	10	15525	1874.36		
Non-diabetics family history positive	18	2619.65	949.67	0.908	0.371
Non-diabetics family history negative	13	1465.36	704.66		

* Difference in Estradiol(pg/ml) is statistically significant at 0.05

THIRD TRIMESTER

GDM with positive family history: The circulatory level of estradiol mean value was 21365.8±1123.781 pg/ml in the gestational diabetics with positive family history. The hormone concentration was 2600.80±627.77 pg/ml in the non-diabetics subjects. An increase in the estradiol levels had been observed in GDM that was almost 08 times greater than the control subjects. It was highly significant statistically (p<0.001). (Table 2).

GDM with negative family history: The circulatory level of estradiol mean value was 21601.16±1689.69 pg/ml in the third trimester gestational diabetics with negative family history. The hormone concentration was 6417.47±1673.92 pg/ml in the non-diabetics normal pregnant subjects with family history negative. A marked increase in the estradiol levels had been observed in GDM that is almost 03 times greater than the control subjects. It was highly significant statistically (p<0.001) (Table 2).

GDM with different family history: The estradiol mean value was 21365.78±1123.78 pg/ml in the third trimester gestational diabetics with positive family history. The hormone concentration was 21601.17±1689.70 pg/ml in the third trimester gestational diabetics subjects with family history negative. No difference in the estradiol levels had been observed in the third trimester gestational diabetics with positive and negative family history. So it was not significant statistically (p value 0.905) (Table 2).

Non-GDM with different family history: The estradiol mean value was 2600.80±627.77 pg/ml in the third trimester non-diabetics with positive family history. The hormone concentration was 6417.47±1673.93 pg/ml in the third trimester non-diabetic subjects with family history negative. A marked increase in the estradiol levels had been observed in the third trimester non-diabetics with negative family history that was almost 2 times greater. So it was significant statistically (p value 0.05) (Table 2).

Table 2: Comparison of Estradiol according to 3rd trimester gestational diabetics and family history.

3rdtrimester Group	N	Mean	SEM	t-test	p-value
Diabetic family history positive	18	21365.8	1123.78	11.81	<0.001*
Non-diabetic family history positive	10	2600.8	627.77		
Diabetic family history negative	12	21601.16	1689.69	6.349	<0.001*
Non-diabetic family history negative	14	6417.47	1673.92		
Diabetics family history positive	18	21365.78	1123.78	0.121	0.905
Diabeticsfamily history negative	12	21601.17	1689.7		
Non-diabetics family history positive	10	2600.8	627.77	1.851	0.050
Non-diabetics family history negative	14	6417.47	1673.93		

* Difference in Estradiol is statistically significant at 0.05

COMPARISON OF 2ND AND 3RD TRIMESTER

GDM with positive family history: The estradiol mean value was 20078.67±767.47 pg/ml in second trimester gestational diabetics with positive family history. The hormone concentration was 21365.78±1123.78 pg/ml in the third trimester gestational diabetics with family history positive. Increase in the estradiol levels had been observed in third trimester gestational diabetics that was 6% greater than the second trimester gestational diabetics. It was not significant statistically (p value 0.371) (Table 3).

GDM with negative family history: The mean value of estradiol was 15525±1874.36 pg/ml in the second trimester

of gestational diabetics with negative family history. The hormone concentration was 21601.17±1689.69 pg/ml in the third trimester of gestational diabetics with family history negative. An increase in estradiol levels had been observed in the third trimester that was almost 39 % greater than the second trimester. So it was highly significant statistically (p value 0.026)(Table 3).

Non GDM with Positive family history: The estradiol mean value was 2619.65±949.67 pg/ml in the second trimester non-diabetics with positive family history. The hormone concentration was 2600.80±627.77 pg/ml in the third trimester. No difference in the estradiol levels had been observed in the second and third trimester non-diabetics with positive family history. So it was not significant statistically (p value 0.989) (Table 3).

Non GDM with negative family history: The estradiol mean value was 1465.356 ± 704.664 pg/ml in the second trimester non-diabetics with negative family history. The hormone concentration was 6417.47 ± 1673.92 pg/ml in the third trimester non-diabetics with family history negative. An increase in the estradiol levels had been observed in the third trimester non- diabetics with negative family history that was almost 04 times greater. So it was highly significant statistically (p value 0.014) (Table 3).

Table 3: Comparison of Estradiol according to 2nd trimester & third trimester gestational diabetics and family history.

Group	N	Mean	SEM	t-test	p-value
Diabetics 2nd trimester family history positive.	15	20078.67	767.47	0.908	0.371
Diabetics 3rdtrimester family history positive	18	21365.78	1123.78		
Diabetics 2nd trimester family history negative	10	15525	1874.36	2.411	0.026*
Diabetics 3rd trimester family history negative	12	21601.17	1689.69		
Non-diabetics 2nd trimester family history positive	18	2619.65	949.67	0.014	0.989
Non-diabetics 3rdtrimester family history positive	10	2600.8	627.77		
Non-diabetics 2nd trimester family history negative	13	1465.356	704.664	2.652	0.014*
Non-diabetics 3rdtrimester family history negative	14	6417.47	1673.92		

*Difference in Estradiol is statistically significant at 0.05

DISCUSSION

The present study elaborates the adaptation and influence of pregnancy on the responses of estrogenin second and third trimesters with and without family history of GDM while comparing with non-GDM state. The state of GDM as may be the result of insulin resistance and other associated mechanisms causing significant hyperglycemia in the pregnancy. Responses of the hormones are varied in the same trisemester with positive and negative family history. Pregnancy is a physiological phenomenon which is divided in to three trimesters each lasting for three months[1]. In which maternal body faces metabolic changes which can be divided into an anabolic and a catabolic phase[21].The first and second trimester of pregnancy corresponds with anabolic phase of pregnancy and is directed at nutrient storage and the buildup of reserves, which are then mobilized in the catabolic phase of third trimester when they are required for fetal growth and to prepare the mother for lactation[19].

It is observed that with increasing trimesters the requirements of nutrients also increases to balance the changes of pregnancy. These changes are brought about by hormones secreted by the placenta, corpus luteum, and maternal organs to maintain the balance between metabolic changes. The catabolic state which is characteristic of late gestation is achieved through changes in insulin production and sensitivity combined with a continuing increase in maternal food uptake[19]. GDM usually becomes apparent during the late phase of pregnancy. It is related with both impaired insulin secretion and hormonal blocking effect son the insulin, a condition referred to as insulin resistance[22].After delivery diabetic symptoms usually disappear[23] .

Estrogen increased 11 times in negative family history pregnancies compared to 8 times increase in positive family history subjects. Thus expression of estrogens seemed to be lower in positive family history. Pregnancy with gestational diabetes mellitus is characterized by insulin resistance which usually begins in the late phase of pregnancy and progresses till the end of the pregnancy .It is observed that placental hormones are major contributor to the insulin-resistant state and this state plays a role in ensuring that the fetus has an good supply of glucose by changing the mother's energy metabolism from carbohydrates to lipids[24]. The present study with analysis of its results has shown that there is more complex mechanism in the role of the placental hormones causing insulin resistance. The results above compared have shown that the different pregnancy hormones play the role variedly.

The hormones profile in the third trimester is in contrast to second semester, unlike second semester estrogen increased 3 and 8 times in negative and positive family history subjects respectively. The response is almost opposite to that of second semester. In the normal pregnancies subjects were categorized in those with positive and negative family history of diabetes/GDM. In these comparisons there are significantly varied responses of the hormones in the comparing categories. Estrogen was increased 78% in positive compared to negative family history subjects in second semester. In third trisemester compared to negative family history all the hormones demonstrated lower expression in the positive family history.

The response of estrogen has also been compared between second and third semester. In GDM subjects the comparison of negative and positive family history did not show conspicuous results however in non-GDM subjects the family history of GDM factor have shown very significant results. Estrogen showed high expression in negative family history subjects. Most of the studies have suggested that two main factors of insulin resistance include increased maternal adiposity and the placental hormonal effects of desensitizing insulin. The fact that

immediately after delivery insulin resistance rapidly decreased which may shows that placental hormones are major contributors.

The present study has revealed that insulin resistance mechanism is not plainly due to the effect of placental hormones collectively. It points out that the mechanisms in GDM insulin resistance may be due to the placental hormones however their expressions are very complex and it provides strong evidence for further investigating the complexity of GDM in different populations. Human chorionic somatomammotropin (HCS) stimulates fetal pancreas for secretion of insulin and inhibits peripheral uptake of glucose in the mother[25]. As the pregnancy advances the size of the placenta increases, so does the production of the estrogen and other hormones, leading to a more insulin-resistant state. In non-diabetic pregnant females, the first and second trimester insulin responses compensate for this reduction in insulin sensitivity, and this is associated with pancreatic β-cell hypertrophy and hyperplasia[25]. However, females who have a deficit in this additional insulin secretory capacity develop GDM.

Gestational diabetes mellitus had been studied in 2nd and 3rd trimesters in relation to the family history[13]as the insulin sensitivity is predominantly influenced in the late stages of pregnancy. As family history effects the trimester factor also influences the metabolic disorder. It is often reported that females with positive family history of diabetes mellitus are at risk of developing the metabolic disorder. So, family history is often related with diabetic risk factors like increasing age, body weight and fat deposition in abdomen[9]. It is likely that the mechanisms that are influenced due to positive and negative family history interact and influence the specific pregnancy hormones.

Estradiol is recognized as the dominant estrogen and is known to be present at high levels during gestation[15]. The production of estrogens during pregnancy occurs as collaboration between the maternal and fetal metabolism[16]. The various metabolites in this process are subsequently converted into estrone and estradiol and secreted back into the maternal circulation[15]. This gives rise to the concept of the fetoplacental unit as a site of hormone production during pregnancy.

Statistically highly significantly variable levels of estrogen in GDM and non-GDM; in different trimester and with or without family history of GDM clearly expound the adaptability in these different states. There is possibility that adaptation in each different situation involve the mechanisms in fetoplacental unit. This point out to investigate GDM for the estrogens in mechanisms of fetoplacental unit.

In conclusion the analysis of the estrogen hormone in present study reveals that estrogen levels in pregnancy are affected variedly in different states of GDM and the estrogen and other hormones are directly responsible for the induction of insulin resistance.

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